FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 10-94)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		**ATTORNEY'S DOCKET NUMBER** 000364.00124 / **U.S. APPLICATION NO.** 10/088113
INTERNATIONAL APPLICATION NO. PCT/CH00/00409	**INTERNATIONAL FILING DATE** 27 July 2000	**PRIORITY DATE CLAIMED** 12 October 1999

TITLE OF INVENTION: Medicament for Treatment of Neuropathies

APPLICANT(S) FOR DO/EO/US: Juerg Lareida

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto
   b. ☐ Has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An **executed** oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98 (w/PTO 1449 and references)
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
20. ☐ Other items or information:

U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NO.
10/088113 Unknown	PCT/CH00/00409	000364.00124

21. ☒ The following fees are submitted:		CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):			
☒ Search Report has been prepared by the EPO or JPO (37 CFR 1.492(a)(5))	$890.00		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1))	$710.00		
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$740.00		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$1,040.00		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT		$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$0.00	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total Claims	7	- 20	0	$18.00	$0.00	
Independent Claims	2	- 3	2	$84.00	$0.00	
☐ MULTIPLE DEPENDENT CLAIM(S) (if applicable)				$280.00	$0.00	
TOTAL OF ABOVE CALCULATIONS =					$890.00	
☒ Reduction by 1/2 for filing by small entity, if applicable.					$445.00	
SUBTOTAL =					$445.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					$0.00	
TOTAL NATIONAL FEE =					$445.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28,3.31). **$40.00** per property					$0.00	
TOTAL FEES ENCLOSED =					**$445.00**	
Amount to be refunded:						
charged:						

a. ☒ A check in the amount of $ 445.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **23-2185** . A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
CUSTOMER NO.: 002779
BLANK ROME COMISKY & MCCAULEY LLP
900 - 17th Street, N.W., SUITE 1000
Washington, D.C. 20006

Signature

NAME	Herbert Cohen
Registration No.	25,109
Date	March 15, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of	)	
	)	
Juerg Lareida	)	
	)	
Serial No. Unknown	)	
(Based on PCT/CH00/00409)	)	
	)	Atty. Dkt. No.: 000364.00124
Filed: Concurrently Herewith	)	
	)	
For: MEDICAMENT FOR TREATMENT OF NEUROPATHIES	)	

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the application as follows:

IN THE ABSTRACT:

Please add the attached Abstract of the Disclosure.

IN THE SPECIFICATION:

Page 1, after the title, please add:

--CROSS REFERENCE TO RELATED APPLICATION

This is a National Phase patent application based on PCT/CH00/00409 filed 27 July 2000 which in turn claims priority of Swiss Application No. 1862/99 filed 12 October 1999, the subject matter of which is incorporated herein by reference.

FIELD AND SUMMARY OF THE INVENTION--

Page 2, line 21, insert:

--DESCRIPTION OF PREFERRED EMBODIMENTS--

Please replace the paragraph beginning at page 2, line 26, with the following rewritten paragraph:

--In accordance with a further embodiment, the invention pertains to the use of compounds of formula (I) and/or their pharmaceutically acceptable salts for therapeutic treatment of neuropathies of the type mentioned above.--

Please delete the paragraph beginning at page 2, line 29.

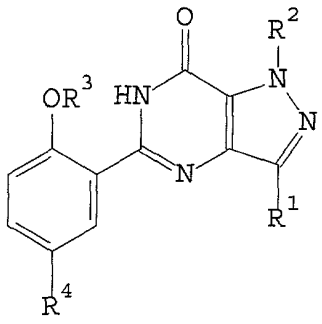
IN THE CLAIMS:

Please change "Patent claims" to --What is Claimed--.

Please cancel claim 4, without prejudice.

Please amend claims 1-3, and 5, as follows:

1. (Amended) A pharmaceutical agent for treatment of neuropathies, comprising a compound of formula (I):



(I)

in which:

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted by halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, possibly substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

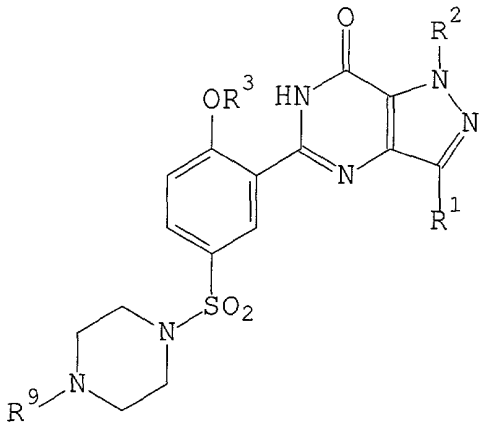
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen, C_{1-4}alkyl, optionally, are substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms; or of a pharmaceutically acceptable salt of such a compound.

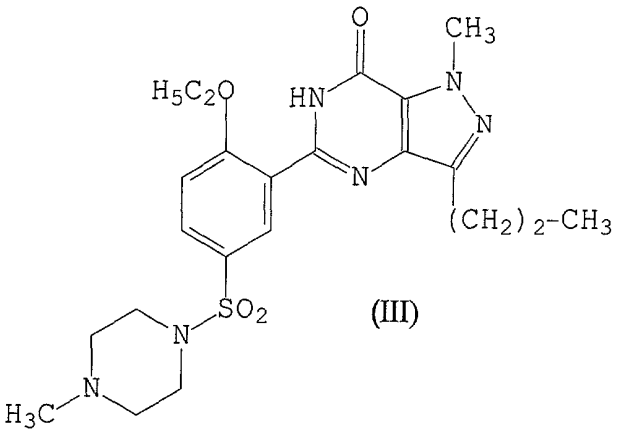
2. (Amended) The pharmaceutical agent according to Claim 1, comprising a compound of formula (Ia):



(Ia)

in which the groups R^1 to R^3 have the meaning specified in Claim 1, and R^9 is an alkyl group having 1 - 4 C atoms which, optionally, are substituted or replaced by halogen; or of a pharmaceutically acceptable salt of such a compound.

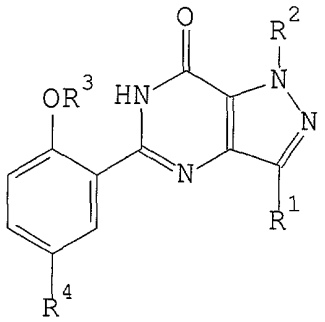
3. (Amended) The pharmaceutical agent according to Claim 1, comprising a compound of formula (III):



(III)

or of a pharmaceutically acceptable salt of such a compound.

5. (Amended) A chemotherapeutic method for treatment of neuropathies characterized by application to a patient of a pharmaceutical agent comprising a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl having 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound.

Please add the following new claims 6, 7 and 8.

6. (New) --The method of claim 5, wherein from 1-100 mg/day of said pharmaceutical agent is administered to a patient being treated.

7. (New) The method of claim 5, wherein from 5-50 mg/day of said pharmaceutical agent is administered to a patient being treated.

8. (New) The method of claim 5, wherein from 25-50 mg/day of said pharmaceutical agent is administered to a patient being treated.--

REMARKS

This Preliminary Amendment is submitted to make clarifying revisions to the specification and claims in accordance with U.S. practice. No narrowing of the claims scope is intended.

In the event there are any questions relating to this Amendment or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney.

Please charge any shortage or credit any overpayment of fees to BLANK ROME COMISKY & MCCAULEY LLP, Deposit Account No. 23-2185 (000364.00124). In the event that a petition for an extension of time is required to be submitted herewith and in the event that a separate petition does not accompany this report, Applicants hereby petition under 37 C.F.R. §1.136(a) for an extension of time for as many months as are required to render this submission timely. Any fee due is authorized above.

Respectfully submitted,

Date: March 15, 2002

BY: _____
Herbert Cohen
Registration No. 25,109

BLANK ROME COMISKY & MCCAULEY LLP
900 - 17th Street, N.W., Suite 1000
Washington, DC 20006
(202) 530-7400 (phone)
(202) 463-6915 (facsimile)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 26 of page 2 has been amended as follows:

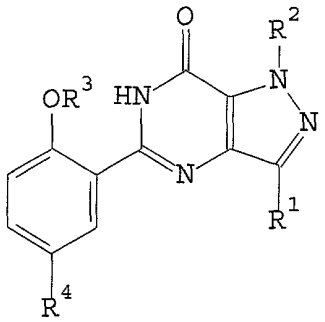
In accordance with a further embodiment, the invention pertains to the use of compounds of formula (I) and/or their pharmaceutically acceptable salts [or production of a pharmaceutical agent]for therapeutic treatment of neuropathies of the type mentioned above.

In the Claims:

Claim 4 has been cancelled.

Claims 1-3 and 5 has been amended as follows:

1. (Amended) A pharmaceutical agent for treatment of neuropathies, [characterized in that it consists, at least in part, of] comprising a compound of formula (I):



(I)

in which:

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted by halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, possibly substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

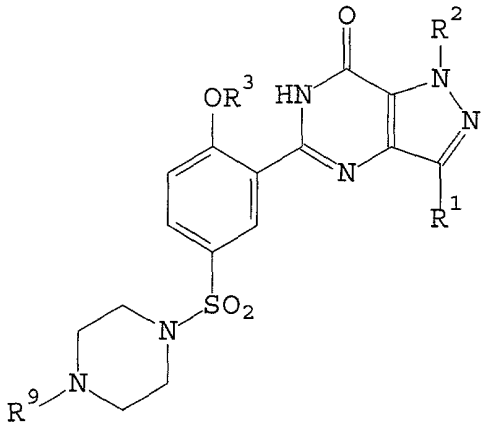
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen, C_{1-4}alkyl, optionally, are substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms; or of a pharmaceutically acceptable salt of such a compound.

2. (Amended) The pharmaceutical agent according to Claim 1, [characterized in that it consists, at least in part, of] comprising a compound of formula (Ia):

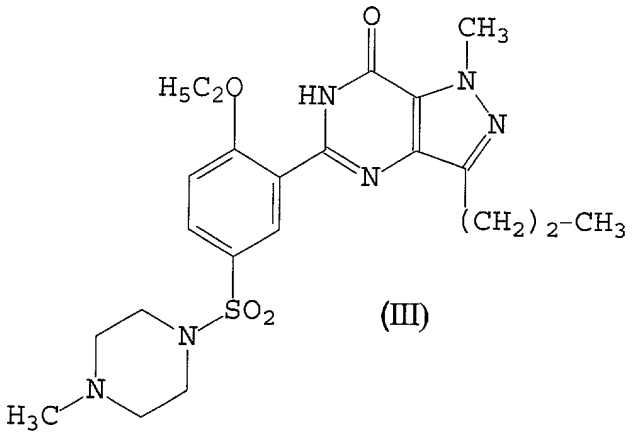


(Ia)

in which the groups R^1 to R^3 have the meaning specified in Claim 1, and R^9 is an alkyl

group having 1 - 4 C atoms which, optionally, are substituted or replaced by halogen; or of a pharmaceutically acceptable salt of such a compound.

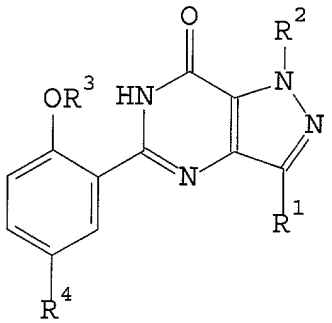
3. (Amended) The pharmaceutical agent according to Claim 1, [characterized in that it consists, at least in part, of] comprising a compound of formula (III):



(III)

or of a pharmaceutically acceptable salt of such a compound.

5. (Amended) A chemotherapeutic method for treatment of neuropathies characterized by application to a patient of a pharmaceutical agent [which consists, at least in part, of] comprising a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl having 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound.

ABSTRACT OF THE DISCLOSURE

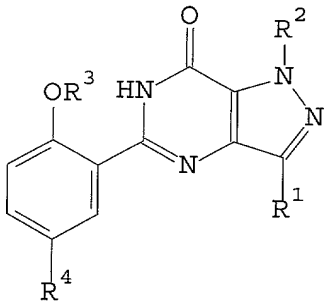
Compounds of formula (I) in which R^1 = C_{1-6} alkyl, optionally halosubstituted; R^2 = H, C_{1-4} alkyl, optionally halosubstituted or replaced by halogen; R^3=C_{2-4} alkyl, optionally halosubstituted; R^4 = $SO_2NR^5R^{\&}$, CO_2R^7 or halogen, C_{2-4} alkenyl; optionally substituted with NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO^2R^7 or halogen, C_{2-4} alkanoyl, optionally substituted with NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 or halogen; R^5 and R^6 = independently H or C^{1-4} alkyl, or, together with the N atom to which they are attached, a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring optionally substituted with one or two C_{1-4} alkyl groups; R^7 = H, C^{1-4} alkyl, optionally fluorosubstituted, and R^8=H,C^{1-3} alkyl or hydroxyalkyl with 1 – 4 C atoms, or the pharmaceutically acceptable salts thereof are useful for the chemotherapeutic treatment of neuropathies.

10/088113
JC13 Rec'd PCT/PTO 15 MAR 2002
PCT/CH00/00409

Medicament for Treatment of Neuropathies

The present invention relates to pharmaceutical agents for treatment of neuropathies, such as, e.g., peripheral diabetic polyneuropathies and gastropareses, as well as general degenerative, toxic, metabolic, ischemic and other autonomous forms of neuropathies in the narrower, namely neurological sense.

Surprisingly, it has been found that compounds of formula (I)



(I)

known, for example, from WO 93/07149 as such and for use as a pharmaceutical agent for cardiovascular disorders, in which

R^1 = C_{1-6}alkyl, optionally substituted by halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted by halogen,

R^3 = C_{2-4}alkyl, optionally substituted by halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms, as well as pharmaceutically acceptable salts of such compounds (I), are suitable for chemotherapeutic treatment of neuropathies of the type mentioned above.

In the above definitions, halogen represents fluorine, chlorine, or bromine, fluorine being preferred.

Compounds which correspond or are analogous to this formula, including its salts, and preparation processes of such compounds and salts are known in the art, e.g. from EP 0 463 756, where they have been proposed for prophylactic or therapeutic treatment of cardiovascular diseases. The cardiovascular activity of formula (I) compounds is based on the fact that these compounds are effective and selective inhibitors for cyclic 3',5'-monophosphate phosphodiesterase (cGMP PDE).

It is not known and - respectively - is improbable on the basis of what is known, that this inhibitor effect plays a significant role in neuropathies of the type mentioned. Also, the efficacy of formula (I) compounds for treatment of neuropathies has, in fact, not been determined on the basis of theoretical considerations, but in an empirical manner, and was neither anticipated nor predictable.

Accordingly, the present invention, in a first embodiment, has for its object a pharmaceutical agent for treatment of neuropathies, characterized in that it consists, at least in part, of at least one compound of formula (I), or at least one pharmaceutically acceptable salt of such a compound, and that it may contain standard auxiliary agents, adjuvants, and carriers, as well as, optionally, additional pharmaceutically active substances.

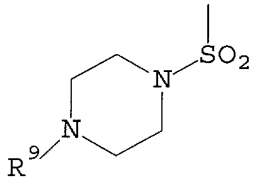
In accordance with a further embodiment, the invention pertains to the use of compounds of formula (I) and/or their pharmaceutically acceptable salts for production of a pharmaceutical agent for therapeutic treatment of neuropathies of the type mentioned above.

In accordance with a third embodiment and to the extent that this is permissible within the framework of national patent laws, the invention is also claimed as a method for therapeutic treatment of neuropathies.

Examples of pharmaceutically acceptable salts of compounds and additional methods of synthesis are also known from the above-noted EP 0 463 756 and, furthermore, from WO 93/07149, as well as from WO 93/06104 and WO 94/05661.

For production of pharmaceutical agents according to the invention, active agents of formula I may be formulated as solid or liquid products with standard adjuvants and carrier substances.

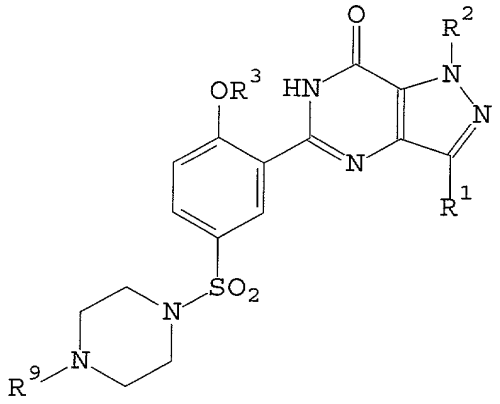
In a preferred group of compounds (I), R^4 represents a group of formula (II):



(II)

particularly if R^1, R^2, R^3, and R^9, respectively, represent alkyl groups with 1 - 4 C atoms, preferably, methyl or ethyl, which, optionally, may be substituted or replaced by halogen, preferably, fluorine.

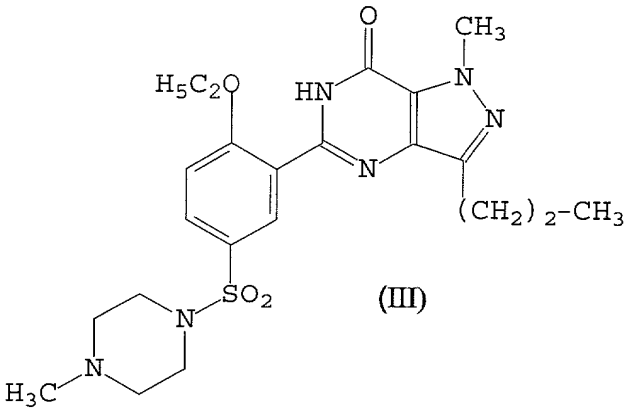
Such compounds correspond to formula (Ia):



(Ia)

in which groups R^1 to R^3 and R^9 have the above-specified meaning.

A preferred specific compound for pharmaceutical agents in accordance with the invention corresponds to formula (III):



(III)

and is the compound known in the art under the generic name sildenafil for treatment of erectile dysfunctions.

Formula (III) compounds and their pharmaceutically acceptable salts can also be prepared in a known manner, e.g., in accordance with the method disclosed in EP 0 463 756.

It is to be expected that effective dosages for treatment of neuropathies will generally be in a similar or lower range as with known medical indications of compounds (1) and (3), respectively, i.e., they will typically be in the range from 1 - 100 mg/day, more specifically, 5 - 50 mg/day, and, typically, 25 - 50 mg/week.

The invention will be explained further by means of examples which are not limiting.

Example 1

A male patient (age 66 years) had been suffering from diabetes mellitus, type 2, for 9 years. While blood glucose values (HbA1c between 6 and 7%) were good, symptoms of a diabetic polyneuropathy appeared, namely vibration sensing of 2/8, no filament sensing, and a reduced hot/cold differentiation. Because of a simultaneous erectile dysfunction he was treated with sildenafil in its commercially available preparation (tablets) at 50 mg/week in a single administration.

Twelve months after start of therapy, a largely normal neurologic situation was reached, namely a vibration sensing of 5/8, intact filament sensing, and hot/cold differentiation. Subjectively, the patient noted disappearance of sensory misperceptions of temperature.

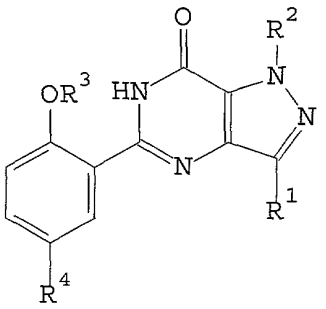
Example 2

A 61-year-old female patient had been suffering from diabetes mellitus, type 1, for about 35 years. Complications included a retinopathy and a painful neuropathy. Under intensified insulin therapy, blood glucose metabolism data were in a sub-optimum range (HbA1c around 8%). Thus, the patient suffered from a painful neuropathy and was treated unsuccessfully with various conventional medicaments.

After medication with sildenafil (50 g/week, each in a single administration of the entire week's dosage), a lasting improvement of symptomatic pain was achieved in the course of the following three months. Objectifiable diagnostic data were improved as well.

Patent claims

1. A pharmaceutical agent for treatment of neuropathies, characterized in that it consists, at least in part, of a compound of formula (I):



(I)

in which:

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted by halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, possibly substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

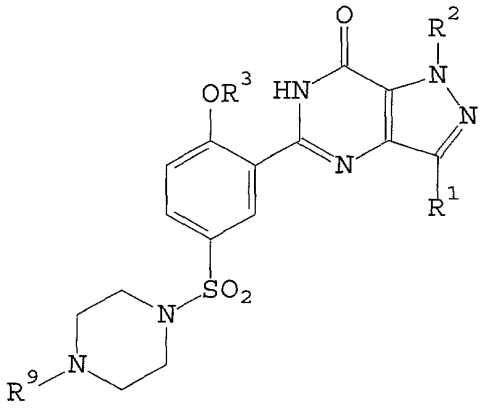
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen, C_{1-4}alkyl, optionally, are substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms; or of a pharmaceutically acceptable salt of such a compound.

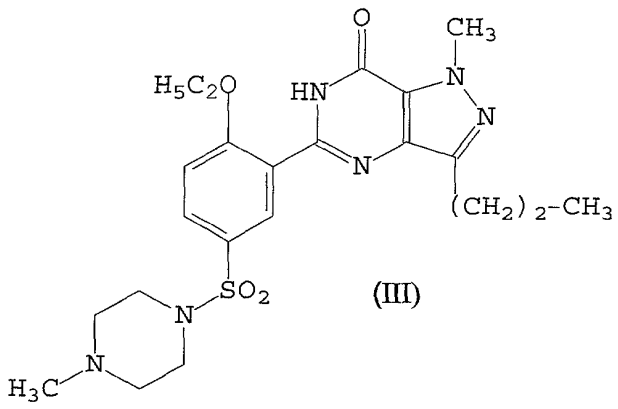
2. The pharmaceutical agent according to Claim 1, characterized in that it consists, at least in part, of a compound of formula (Ia):



(Ia)

in which the groups R^1 to R^3 have the meaning specified in Claim 1, and R^9 is an alkyl group having 1 - 4 C atoms which, optionally, are substituted or replaced by halogen; or of a pharmaceutically acceptable salt of such a compound.

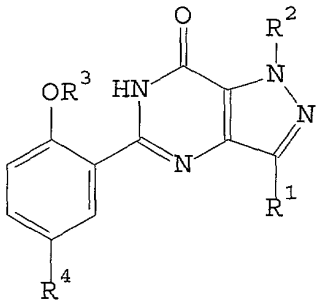
3. The pharmaceutical agent according to Claim 1, characterized in that it consists, at least in part, of a compound of formula (III):



(III)

or of a pharmaceutically acceptable salt of such a compound.

4. A use of compounds of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

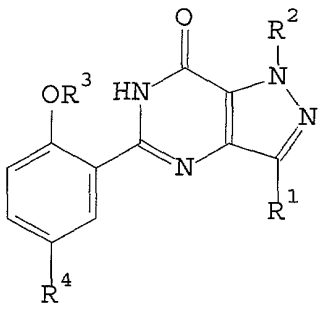
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound for production of a pharmaceutical agent for treatment of neuropathies.

5. A chemotherapeutic method for treatment of neuropathies characterized by application to a patient of a pharmaceutical agent which consists, at least in part, of a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl having 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
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(81) Bestimmungsstaaten *(national)*: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.

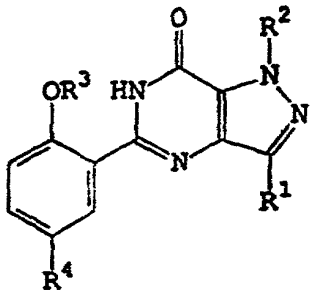
(84) Bestimmungsstaaten *(regional)*: europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht:
— *Mit internationalem Recherchenbericht.*

[Fortsetzung auf der nächsten Seite]

(54) Title: MEDICAMENT FOR TREATMENT OF NEUROPATHIES

(54) Bezeichnung: ARZNEIMITTEL ZUR BEHANDLUNG VON NEUROPATHIEN



(I)

(57) Abstract: Compounds of formula (I) in which R^1 = C_{1-6} alkyl, optionally halosubstituted; R^2 = H, C_{1-4} alkyl, optionally halosubstituted or replaced by halogen; R^3 = C_{2-4} alkyl, optionally halosubstituted; R^4 = $SO_2NR^5R^6$, CO_2R^7 or halogen, C_{2-4} alkenyl, optionally substituted with NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO^2R^7 or halogen, C_{2-4} alkanoyl, optionally substituted with NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 or halogen; R^5 and R^6 = independently H or C^{1-4} alkyl, or, together with the N atom to which they are attached, a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring optionally substituted with one or two C_{1-4} alkyl groups; R^7 =H, C^{1-4} alkyl, optionally fluorosubstituted, and R^8 =H, C^{1-3} alkyl or hydroxyalkyl with 1 - 4 C atoms, or the pharmaceutically acceptable salts thereof are useful for the chemotherapeutic treatment of neuropathies.

(57) Zusammenfassung: Verbindungen der Formel (I), in der R^1 = C_{1-6}-Alkyl, gegebenenfalls mit Halogen substituiert, R^2 = Wasserstoff, C_{1-4}-Alkyl, gegebenenfalls mit Halogen substituiert oder durch Halogen ersetzt, R^3 = C_{2-4}-Alkyl, gegebenenfalls mit Halogen substituiert, R^4 = $SO_2NR^5R^6$, CO_2R^7 oder Halogen, C_{2-4}-Alkenyl, gegebenenfalls substituiert mit NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 oder Halogen, C_{2-4}-Alkeyl, gegebenenfalls substituiert mit NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 oder Halogen, C_{2-4}-Alkanoyl, gegebenenfalls substituiert mit NR^5, R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 oder Halogen, R^5 und R^6 unabhängig voneinander Wasserstoff oder C_{1-4}-Alkyl bedeuten oder zusammen mit dem Stickstoffatom, an dem sie hängen, einen Pyrrolidino-, Piperidino-, Morpholino-, 4-(NR^8)-1-Piperazinyl- oder 1-Imidazolylring bedeuten, der gegebenenfalls mit ein oder zwei C_{1-4}-Alkylgruppen substituiert ist, R^7 = Wasserstoff, C_{1-4}-Alkyl, gegebenenfalls mit Fluor substituiert, und R^8 = Wasserstoff, C_{1-3}-Alkyl oder Hydroxyalkyl mit 1 - 4 C-Atomen bedeutet, sowie die pharmazeutisch akzeptablen Salze solcher Verbindung eignen sich zur chemotherapeutischen Behandlung von Neuropathien.

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ATTORNEY'S DOCKET NO._____

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **MEDICAMENT FOR TREATMENT OF NEUROPATHIES**

the specification of which

- ☐ is attached hereto
- ☐ was filed on 27 July 2000 as United States Application Number or PCT International Application Number PCT/CH 00/00409 and (if applicable) was amended on _____.

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NUMBER	COUNTRY	(DAY/MONTH/YEAR FILED)	PRIORITY CLAIMED
1862/99	Switzerland	12 October 1999	Yes

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application, or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NUMBER	FILING DATE	STATUS -- PATENTED, PENDING, ABANDONED

Declaration for Patent Application (Continued)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: Herbert Cohen, Reg. No. 25,109; Victor M. Wigman, Reg. No. 25,201, George C. Myers, Jr., Reg. No. 27,040; Donald R. Greene, Reg. No. 22,470; Michael C. Greenbaum, Reg. No. 28,419; Charles R. Wolfe, Jr., Reg. No. 28,680; Michael D. White, Reg. No. 32,795; Brian Jones, Reg. No. 37,857; David J. Edmondson, Reg. No. 35,126; Denise C. Lane, Reg. No. 42,780; Peter Weissman, Reg. No. 40,220; Nicholas Bromer, Reg. No. 33,478 and Rafael Perez, eg. No. 46,041.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name): Juerg LAREIDA	
Signature: X	Date: X 18.2.02
Residence: Vordere Vorstadt 16, 5000 Aarau, Switzerland CHX	Citizenship: Switzerland
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Full name of second joint inventor (given name, family name):	
Signature:	Date:
Residence:	Citizenship:
Mailing Address:	
Full name of third joint inventor (given name, family name):	
Signature:	Date:
Residence:	Citizenship:
Mailing Address:	
Full name of fourth joint inventor (given name, family name):	
Signature:	Date:
Residence:	Citizenship:
Mailing Address:	

o Additional Inventors on next page. (check box if applicable)